UNIVERSITY OF CALIFORNIA,
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Comparison of Oncological Outcomes and Cost of Adjuvant Radiation versus Observation for Post-Radical Prostatectomy Patients

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

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DEDICATION

To my family, committees, colleagues and friends

in recognition of their support

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LIST OF ABBREVIATIONS

RP	: Radical prostatectomy
EBRT	: External beam radiation therapy
ADT	: Androgen deprivation therapy
RARP	: Robot-assisted radical prostatectomy
BCR	: Biochemical recurrence
PSA	: Prostate-specific antigen
SVI	: Seminal vesicle invasion
EPE	: Extraprostatic extension
ART	: Adjuvant radiotherapy
NCCN	: National Comprehensive Cancer Network
RCT	: Randomized control trial
SWOG	: Southwest Oncology Group
EORTC	: European Organization for Research and Treatment of Cancer
OM	: Overall mortality
PCSM	: Prostate cancer specific mortality
NED	: No evidence of disease
SRT	: Salvage radiotherapy
QALY	: Quality-adjusted life year
RADICALS	: Radiotherapy and Androgen Deprivation in Combination after Local Surgery
RTOG	: Radiation Therapy Oncology Group
SEER	: The Surveillance, Epidemiology, and End Results

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ABSTRACT OF THE THESIS

Comparison of Oncological Outcomes and Cost of Adjuvant Radiation versus Observation for Post-Radical Prostatectomy Patients

By

Huang-Wei Su

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2019

Professor Thomas E. Ahlering, Chair

Objective: To analyze the oncological outcomes of "at-risk" men with Prostate cancer (PC) following radical prostatectomy who were managed without versus with adjuvant radiation therapy (ART). Additionally a cost comparison will be conducted between radiotherapy and observation groups.

Patients and Methods: 1500 men who underwent robot-assisted radical prostatectomy (RP) and no adjuvant radiation therapy at UC Irvine constitute the comparator group, (Observation group) of men who had a RP for prostate cancer and managed without ART. Observation patients with no PSA follow-up or who had pre-operative treatment were excluded. All data was prospectively collected and retrospectively analyzed in the observation group. Two comparator groups of men who received ART were selected from two randomized control trials (SWOG 8794 and EORTC 22911) and separately analyzed against the UCI observation group. Outcomes assessed in the analysis include Biochemical recurrence (BCR), metastasis-free survival, prostate cancer specific mortality (PCSM) and Overall survival. Kaplan-Meier analysis was utilized

to compare outcomes with previous randomized control trials. Medicare reimbursement rates were used to estimate cost of secondary interventions.

Results: 364 patients were selected by SWOG 8794 inclusion criteria. After adjusting by proportion of Gleason score and pathological stage, the UCI observation cohort had non-inferior outcomes with metastasis-free and overall survival rate than the trial. Also, analysis in 368 men who were qualified by EORTC 22911 inclusion criteria demonstrated the similar non-inferior results in overall survival and cancer-specific survival rate. Cost per patient in the RCTs was $26,343 for ART groups and $7,874 in the RCT control groups after considering primary, secondary complication treatment expenses versus UCI only $3,544 per patient.

Conclusion: Radiation-naïve patients had non-inferior oncological outcomes as compared to men receiving ART. The expense of ART is three to seven times higher than radiation-naïve men. Decision of early radiation treatment should be re-evaluated because of the lack of mortality benefit, side effects of radiotherapy and cost.

I. INTRODUCTION

1. Background

Prostate cancer is the most common cancer and the second leading cause of cancer death in men. [1] Radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy, chemotherapy, and androgen deprivation therapy (ADT) are treatment options for these patients. [2] One common way to manage prostate cancer is via robot-assisted radical prostatectomy (RARP). For those patients who undergo radical prostatectomy, the incidence rate of biochemical recurrence (BCR) is about 15-25%. [3] BCR is an important outcome post-RP and is identified by prostate-specific antigen (PSA) of 0.2 ng/mL or greater on 2 consecutive tests. [4] Since the early 1990s, adjuvant radiation therapy (ART) has been recommended following RP for men believed at increased risk for BCR due to positive surgical margins, extraprostatic disease (pathologic T3 disease) and/or high-grade (Gleason 8-10) disease. [5] ART is often used in these patients who have adverse pathological features in effort to decrease risk of recurrence. [6] In addition to ART, ADT or chemotherapy are often considered in conjunction for these post-operative patients.

2. Trial review and major consensus on radiotherapy

Based on the National Comprehensive Cancer Network (NCCN) guidelines, ART is advocated to post-operative patients when they have any combination of poor pathological characteristics (i.e. seminal vesicle invasion (SVI), extraprostatic extension (EPE), positive surgical margins or higher Gleason scores). [6] Three randomized control trials (RCT) of ART versus observation present evidence that adjuvant radiotherapy could improve PSA control. However, only one showed benefit on overall and prostate cancer specific survival. The findings of these trials are summarized in Table 1. [3, 14]

Table 1: Major 2 trials on post-operative adjuvant radiotherapy

Trial	Study design	Conclusion	10-yr BCR-free rates	10-yr Metastasis-free	10-yr Overall survival
U.S. SWOG 8794	pT2 / positive surgical margins or pT3 with/without positive surgical margin	Benefits BCR, metastasis-free and overall survival rates	PSA relapse (PSA>0.4) ART vs. observation: 64% vs. 34.9%; p<0.01	ART vs. observation:71 % vs. 61%; p=0.016	ART vs. observation: 74% vs. 66%; p=0.023
Europe EORTC 22911	pT2-3 with/without positive surgical margin	Benefits BCR ; No benefit in metastasis-free, PCSM or overall survival.	ART vs. observation: 60.6% vs. 41.4%; p<0.0001	ART vs. observation:76.5 % vs. 71.3%; No significant	ART vs. observation: 76.9% vs. 80.7%; No significant

2.1 The American Trial, SWOG 8794

The Southwest Oncology Group (SWOG) 8794 trial recruited 425 patients with pT2 disease with positive surgical margins or pT3 with or without positive surgical margins between 1988 and 1997. They then randomized their patients to ART versus observations. Metastasis-free and survival rate were their primary endpoints. For their results, 10-year metastasis-free rate was 71% in the ART group compared with 61% in observation group (HR=0.7; P=0.016). Also, 10-year survival rates were 74% and 66% for ART and observation (HR=0.72; P= 0.023). Both endpoints showed statistically significant improvement in the ART group but only had 1.9 years difference in overall survival and 1.8 years difference in metastasis between two groups. Coincidentally, their adjuvant radiation therapy group began the trial at an average of 1.8 years older than the observation group.

To conclude, they found that ART decreased time to PSA progression. However, there was a significant 24% general complication rate in the ART group, compared to only 12% in the observation patients (P=0.002). For example, both rectal and urinary toxicity had higher chance of happening in the ART group. [3, 7-9] These findings suggest that ART does not come at a nominal cost to these patients.

2.2 The European Trial, EORTC 22911

1005 patients with pT2-3 N0 with or without positive surgical margins were included in the European Organization for Research and Treatment of Cancer (EORTC) 22911. Their primary outcome, BCR-free rate was significantly different between the ART versus observation group; however, they could not identify improvement on overall survival, distant metastasis, or prostate cancer specific mortality. Similar to evidence from the SWOG trial, EORTC also had a higher rate of side effects in their treatment group. According to the Late Radiation Morbidity Scoring Scheme of the Radiation Therapy Oncology Group, late side effects were measured for patients and Grade 3 toxicity incidence rates in ART and observation group were 4.2% and 2.6%, respectively. [3, 7, 10-11] Again, these findings suggest significant reduction in quality of life for patients receiving ART; in EORTC, this should be weighed against the lack of long-term benefit to overall survival, distant metastasis or prostate cancer specific mortality.

3. Specific aims

Because of the above two major RCTs, current guidelines promote ART for patients with poor pathological features (i.e. SVI, EPE, positive surgical margins or higher Gleason scores). They state that better PSA control could reduce risk of recurrence but there is a lack of evidence to support benefit to long-term metastasis and overall mortality. [12-14]

Despite suggestion from guidelines, ART is not often recommended by these characteristics alone by many clinicians for control of PSA because the disparity between the two trials. A key determining factor continues to be an increase in the risk of side effects such as gastrointestinal or genitourinary toxicity. This is an especially pertinent consideration since ART only had advantage on BCR rate and not on long-term survival. [15] In this regard, we seek to assess the effect of adjuvant radiation therapy for reducing risk of recurrence, metastatic progression, PCSM or overall mortality. We will then compare the RCT findings to a matched "at-risk" UCI-cohort of radiation-naïve patients in order to perform a comparison of oncological outcomes. Finally, we conduct a cost analysis of adjuvant radiation versus active surveillance medically related expenses.

II. PATIENT SELECTION AND METHODS

1. Literature review

SWOG 8794 and EORTC 22911 are major trials that emphasize the benefit of ART in slowing PSA progression. We will use their patient demographics and Kaplan-Meier estimates to compare oncologic outcomes with an observation cohort of radiation-naïve patients. Also, articles related to adverse events, side effects, and cost were also reviewed.

2. Outcomes analysis and patient selection

For outcomes analysis, our data were collected and recorded to an electronic spreadsheet under approved institutional review board protocol and in accordance with the Health Information Portability and Accountability At. Every patient who underwent RARP as primary treatment for localized prostate cancer between 2002 and 2015 were included (N=1500). Patients without PSA follow-up or had any pre-operative treatments were excluded (N=40). All patients' information was prospectively maintained and the latest date of follow-up was obtained in order to calculate the median follow-up years. To date, we have been screened all data and formed a research database for comparison and analysis.

In outcomes analysis, the observation patients group consisted of the above 1500 patients, compared ad-hoc with previous trials. In order to test patient similarity, we applied each trial's inclusion and exclusion criteria to our patient group and create the demographic tables. Figure 1a and 1b are the process graph for using SWOG 8794 and EORTC 22911 to choose patients.

Figure 1a: Patient selection by SWOG 8794 inclusion criteria

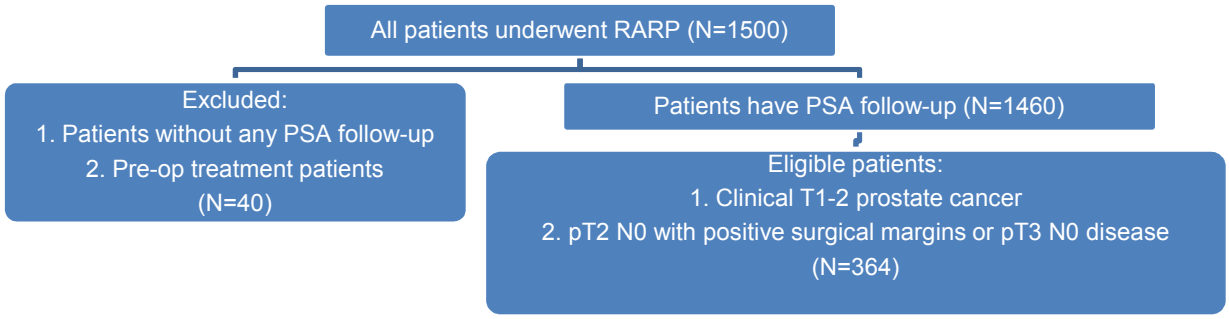
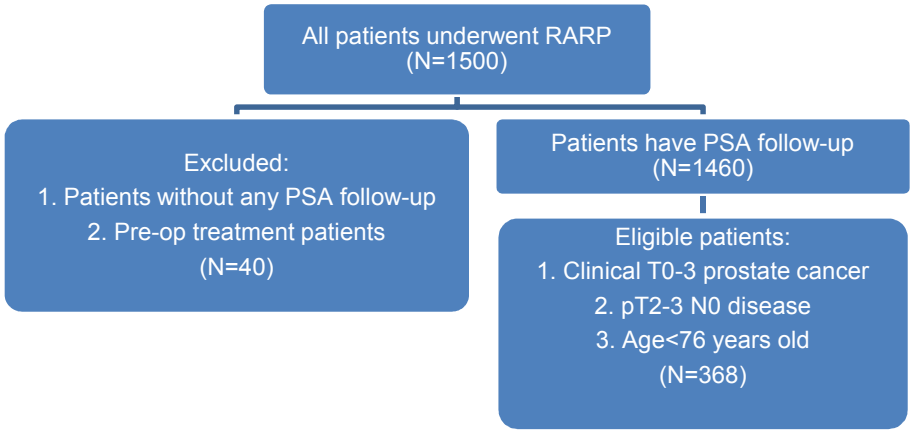


Figure 1b: Patient selection by EORTC inclusion criteria



3. Cost analysis

The cost analysis model for estimating the variation of patient's cost on follow-up treatment was modeled after Showalter and associates' [2011] publication in Annals of oncology]. Figure 2 depicts the treatment schema used to estimate the expense for ART and no ART group in the two RCTs. Assumptions of cost were collected and listed in Table 2. Cost estimates for ART, salvage radiotherapy (SRT), hormonal therapy and management of complications were also included in the table. Rectal bleeding and urinary stricture were considered as major complications for post-radiation patients. Finally, Medicare reimbursement rates were used to assess the treatment of radiation, gastrointestinal or

genitourinary toxicity. Probabilities of side effects, SRT and hormonal therapy were directly obtained from the trials. [8, 10, 16, 22]

Figure 2: Treatment schema for post-operative patient

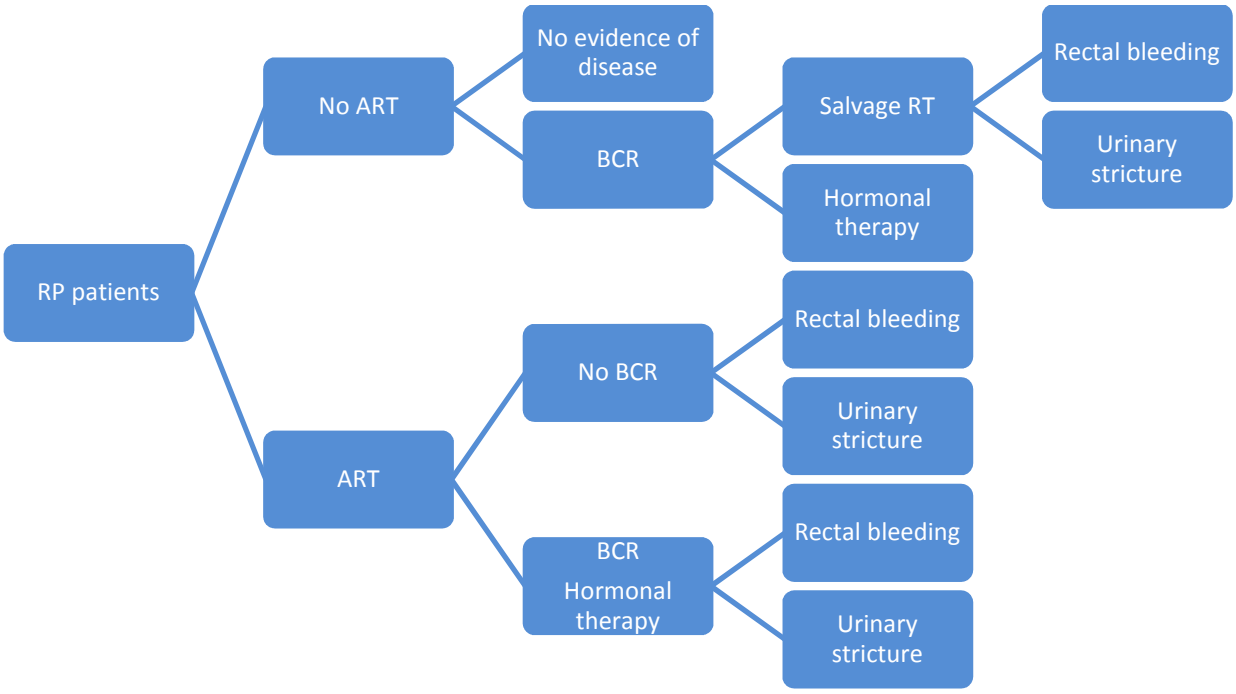


Table 2: Cost values in the treatment schema

Cost values	Value	Reference
ART	$24,548	Luo et al. [23]
SRT	$16,755	Luo et al. [23]
Rectal bleeding treatment	$2,660	2010 Medicare reimbursement rates
Urinary stricture treatment	$4,648	2010 Medicare reimbursement rates
Hormonal therapy	$8,991	Krupski et al. [24]

*The low and high values were calculated by one way sensitivity analyses

Table 2b: Probability values in SWOG 8794 trial

Probability	SRT	Rectal bleeding treatment	Urinary stricture treatment	Hormonal therapy
Observation	0.33	0	0.095	0.21
ART	N/A	0.033	0.178	0.1

*N/A: Not applicable

4. Statistical Analysis

All statistical analysis was conducted in SPSS v 14 © IBM. Age, ethnicity, pathologic Gleason score, PSA data and pathological features (i.e. SVI, EPE, positive surgical margins or high-risk Gleason scores) were displayed in demographic tables. Continuous variables were reported using mean; categorical variables were reported with count and proportions. Rates of each adverse pathological feature, overall mortality, metastasis-free survival and PCSM were calculated and compared between NED and BCR groups. Kaplan-Meier models were built to compare 5 year rate of BCR-free, overall mortality, metastasis-free rate, and PCSM between each of the two randomized control trials and our cohort of observation / radiation-naïve patients. In addition, we adjusted our patients by both trials' proportion of Gleason score and pathological stage in order to have more similarity on patient's progression. Chi-square test was utilized to compare the proportion between RCTs and UCI patients before and after adjustment. [8, 16]

III. RESULTS

1. Baseline characteristics

1.1 The American Trial, SWOG 8794

364 patients in our clinic were selected by SWOG 8794 criteria in Table 3. Compared to the trial cohort, a few key differences should be noted. First, because patients who had treatments before surgery was one of our exclusion criteria, we did not have patients with pre-operative hormonal therapy. Second, most of our patient's ethnicity was white. Third, regarding pathological features, only 3.6% of our patients had extracapsular extension with seminal vesicle invasion or positive surgical margin with seminal vesicle invasion. Due to these differences, the SWOG trial had disproportionate rate of Grade 2-6 and 8-10 favoring ART group. This difference would favorably impact Metastasis-Free survival. Finally, for patient's pre-op and post-op PSA, UC Irvine's observation group had lower mean value.

Table 3: Baseline characteristics for SWOG 8794 and our patients

	Observation	Adjuvant Radiation	UCI Patient (Unadjusted)	UCI patient (Adjusted)
No. subjects	211	214	364	80
Median age	65.8	64.1	63	62
Median yrs follow-up	12.5	12.7	5.4	6.9
% Pre-op hormonal therapy use:				
Yes	8	9	0	0
No	92	91	100	100
% Ethnicity				
White	67	72	98.1	95
Black	20	19	0.8	2.5
Other	13	9	1.1	2.5
% Pathological extent of disease:				
Extracapsular extension or positive margin	68	67	86.5	66
Seminal vesicle invasion	11	10	9.9	18

Both	21	23	3.6	16
No. with Gleason score data	159	166	364	80
% Gleason score:				
2–6	46	57	11	50
7	38	34	71.7	33
8–10	16	9	17.3	17
No. with pre-op PSA data	154	148	364	80
% Pre-op PSA:				
Less than 10 ng/ml	52	47	80.2	76.3
10 ng/ml or Greater	48	53	19.8	23.7
No. with post-op PSA data	186	190	364	80
% Post-op PSA:				
Less than 0.2 ng/ml	68	65	94.2	92.5
0.2 ng/ml or Greater	32	35	5.8	7.5

1.2 The European Trial, EORTC 22911

EORTC had no internal demographic issues. Table 4 compares our patients with that of the EORTC trial. Again, key differences to note are as follows. First, the median age in our observation patient cohort was 63 and we did not have patients who had WHO performance status higher than 0. WHO performance grade 0 was defined that patient could perform all normal activity without restriction. [17] Second, UC Irvine had less aggressive pathology when compared to the EORTC trial, based on percentage difference in high Gleason score group (8-10)

Table 4: Baseline characteristics for EORTC 22911 and our patients

	Wait and See(N=503)	Irradiation(n=502)	Total(n=1005)	UCI(N=368) (Unadjusted)	UCI (N=252) (Adjusted)
Median age (years)	65	65	65	63	63
WHO performance status*					
0	473(94%)	471(93.8%)	944(93.9%)	368(100%)	252(100%)
1	29(5.8%)	26(5.2%)	55(5.5%)	0(0%)	0(0%)

2	1(0.2%)	2(0.4%)	3(0.3%)	0(0%)	0(0%)
Missing	0	3(0.6%)	3(0.3%)	0(0%)	0(0%)
Clinical tumor stage					
cT0	2(0.4%)	4(0.8%)	6(0.6%)	0(0%)	0(0%)
cT1	84(16.7%)	87(17.3%)	171(17%)	204(55.4%)	142(56.3%)
cT2	337(67%)	316(62.9%)	653(65%)	141(38.3%)	91(36.1%)
cT3	80(15.9%)	94(18.7%)	174(17.3%)	23(6.3%)	19(7.5%)
cTx	0(0%)	1(0.2%)	1(0.1%)	0(0%)	0(0%)
Clinical nodal status					
cN0	494(98.2%)	486(96.8%)	980(97.5%)	368(100%)	252(100%)
cNx	9(1.8%)	16(3.2%)	25(2.5%)	0(0%)	0(0%)
Metastatic status					
M0	500(99.4%)	494(98.4%)	994(98.9%)	363(98.6%)	246(97.6%)
M1	0	1(0.2%)	1(0.1%)	5(1.4%)	6(2.4%)
Mx	3(0.6%)	7(1.4%)	10(1%)	0(0%)	0(0%)
Median PSA before surgery (µg/L)	12.5	12.3	12.4	6.2	6.5
PSA after surgery before irradiation					
≤0·2 µg/L	345(68.6%)	353(70.3%)	698(69.5%)	353(96%)	239(94.8%)
>0·2 µg/L	157(31.2%)	144(28.7%)	301(29.9%)	15(4%)	13(5.2%)
Unknown	1(0.2%)	5(1%)	6(0.6%)	0(0%)	0(0%)
Pathological nodal status					
pN0	501(99.6%)	495(98.6%)	996(99.1%)	209(56.8%)	148(58.7%)
pN+	0	2(0.4%)	2(0.2%)	0(0%)	0(0%)
pNx	2(0.4%)	2(0.4%)	4(0.4%)	159(43.2%)	104(41.3%)
Missing	0	3(0.6%)	3(0.3%)	0(0%)	0(0%)
WHO histopathological grade**					
G1	57(11.3%)	69(13.7%)	126(12.5%)	39(10.6%)	35(14%)
G2	327(65%)	303(60.4%)	630(62.7%)	266(72.3%)	154(61%)
G3	116(23.1%)	122(24.3%)	238(23.7%)	63(17.1%)	63(25%)
Gx	3(0.6%)	5(1.0%)	8(0.8%)	0(0%)	0(0%)
Missing	0	3(0.6%)	3(0.3%)	0(0%)	0(0%)

Pathological T stage					
pT2(R1)	79(15.7%)	84(16.7%)	163(16.2%)	52(14.1%)	52(20%)
pT3a	296(58.8%)	288(57.4%)	584(58.1%)	267(72.6%)	151(60%)
pT3b	128(25.4%)	128(25.5%)	256(25.5%)	49(13.3%)	49(20%)
Ineligible	0	2(0.4%)	2(0.2%)	0(0%)	0(0%)
Pathological risk factors					
Capsule perforation	397(78.9%)	377(75.1%)	774(77%)	267(72.6%)	151(59.9%)
Seminal vesicle invasion	128(25.4%)	128(25.5%)	256(25.5%)	48(13%)	49(19.4%)
Positive surgical margin	317(63%)	312(62.2%)	629(62.6%)	137(37.2%)	100(39.7%)

*WHO performance status: 0 (Able to perform all normal activity without restriction), 1 (Restricted in physically strenuous activity but ambulatory and able to carry out light work), 2 (Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
**WHO histopathological grade: G1 (Gleason score 2-6), G2 (Gleason score 7), G3 (Gleason score 8-10) [17]

2. Comparison with previous RCTs (SWOG 8794 and EORTC 22911)

2.1 The American Trial, SWOG 8794

In Table 5a, 364 (25%) patients were indicated to undergo ART. BCR occurred in 120 (33%) patients. Median follow-up data was 5.2 years for the patients and 83% had follow-up PSA over 2 years. We only had 5 patients who underwent ART and 38 patients who underwent SRT. OM was similar between NED and BCR group: 18 (49%) and 19 (51%), respectively. In comparison to survival rate with previous trials, we had lower OM (2.5%) and PCSM (0.7%) rates. After adjusting by proportion of Gleason score and pathological stage in the trial, we used Kaplan-Meier to estimate the 5 years metastasis-free and survival rate graph in figure 3.

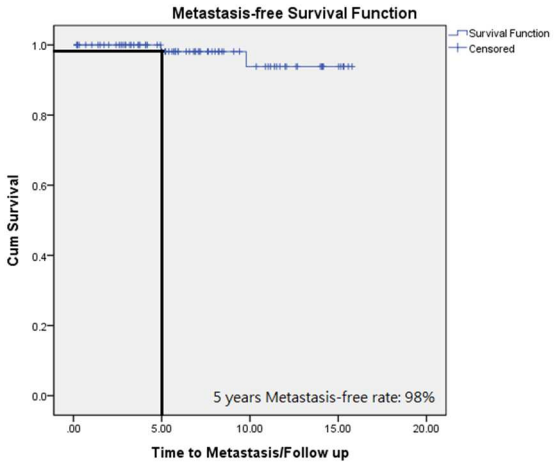
Table 6a was the unadjusted and adjusted clinical outcomes compared between the trial and our UC Irvine cohort of observation patients. For status of metastasis, besides the patients who had metastasis in bone scan, we also assumed patients who died of prostate cancer within 7 years of the radical prostatectomy had metastasized. Even with adjustment of our patient cohort to match the proportion of high-risk Gleason score and high-volume pathological stage in the trial, we had a 98% metastasis-free rate [Unadjusted and adjusted p-value<0.0001]. Comparison of proportion on unadjusted and adjusted metastasis-free and overall survival rates were calculated in table 6a, 7a and 7b.

Table 5a: Patient Pathological Features meeting SWOG 8794 inclusion criteria

N=1460	Total patients	Tx per SWOG	pT3b	pT3	(+)SM	Tx w/ ART	Tx w/ SRT	Mortality	PCSM
Total	1460	364	51	261	52	5	38	37	10
% of 1460	N/A	24.93%	3.49%	17.88%	3.56%	0.34%	2.60%	2.53%	0.68 %
NED	1141	244	20	183	41	2	0	18	0
% of total	78.15%	67.03%	39.22%	70.11%	78.85%	40%	0%	48.65%	0%
BCR	319	120	31	78	11	3	38	19	10
% of total	21.85%	32.97%	60.78%	29.89%	21.15%	60%	100%	51.35%	100%

*N/A: Not applicable

Figure 3: Adjusted Kaplan-Meier of our patient cohort, per SWOG 8794 inclusion criteria (Metastasis-free and Overall survival rate)



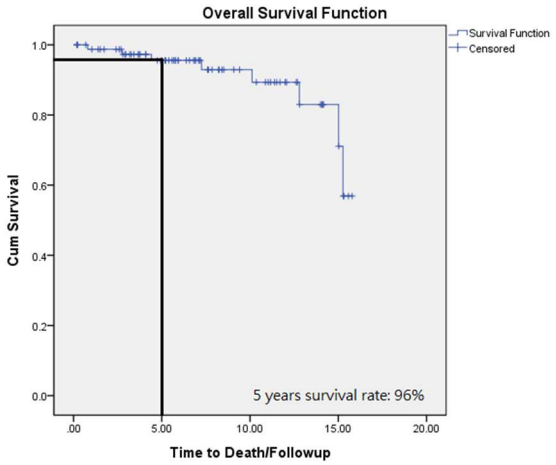


Table 6a: Outcomes comparison with SWOG 8794 (Metastasis-free and Overall survival rate)

	SWOG 8794		Our patients	
	ART group	No ART group	Unadjusted	Adjusted
Inclusion criteria	• RP patients with Clinical T1–2 prostate cancer • Pathological T3 disease with at least one of the adverse features			
5 years Metastasis-free rate	85%	81%	98%	98%
5 years Survival rate	89%	88%	94%	96%

Table 7a: Summary table on comparison of proportion (Unadjusted Metastasis-free and Overall survival rate)

	5 yrs Metastasis-free rate		5 yrs Overall Survival	
SWOG				
ART group	85%		89%	
No ART group		81%		88%
UCI				
Unadjusted	98%	98%	94%	94%
Unadjusted p	<0.0001	<0.0001	0.013	0.003

Table 7b: Summary table on comparison of proportion (Adjusted Metastasis-free and Overall survival rate)

	5 yrs Metastasis-free rate		5 yrs Overall Survival	
SWOG				
ART group	85%		89%	
No ART group		81%		88%
UCI				
Adjusted	98%	98%	96%	96%
Adjusted p	<0.0001	<0.0001	0.0003	<0.0001

2.2 The European Trial, EORTC 22911

368 (25%) patients from our observation cohort fell within EORTC inclusion criteria and were compared to the EORTC trial. All distributions for each variable in table 5b were almost identical to the SWOG trial. In our patients within 5.3 median follow-up years, 124 (34%) patients had BCR and 7 (0.5%) of them went through ART. Only 38 (2.6%) patients died in total and both No evidence of disease (NED) and BCR groups had equal OM. Figure 3b showed that BCR-free, survival and PCSM-survival graphs were made by Kaplan-Meier and tested our result in 5 years. We also adjusted our patient cohort by pathologic Gleason score and pathological stage before applying survival analysis.

As depicted in table 6b, we had a lower percentage of BCR-free rate (67%) compared with ART group (79%) in the trial. However, we still had high survival (93%) and PCSM-survival rate (97%). In table 8a and 8b, EORTC trial had significant difference with UCI in unadjusted and adjusted BCR-free rate. However, there were no differences between trial and UCI in overall survival and cancer-specific survival rate.

Table 5b: Patient Pathological Features meeting EORTC 22911 inclusion criteria

N=1460	Total patients	Tx per EORTC	pT3b	pT3	(+)SM	Tx w/ ART	Tx w/ SRT	Mortality	PCSM
Total	1460	368	49	267	52	7	43	38	13
% of 1460	N/A	25.21%	3.36%	18.29%	3.56%	0.48%	2.95%	2.60%	0.89%

NED	1141	244	20	183	41	2	0	19	0
% of total	78.15%	66.30%	40.82%	68.54%	78.85%	28.57%	0%	50%	0%
BCR	319	124	29	84	11	5	43	19	13
% of total	21.85%	33.70%	59.18%	31.46%	21.15%	71.43%	100%	50%	100%

*N/A: Not applicable

Figure 3b: Kaplan-Meier of our patient cohort, per EORTC 22911 inclusion criteria (BCR-free, Overall survival and Cancer-specific survival)

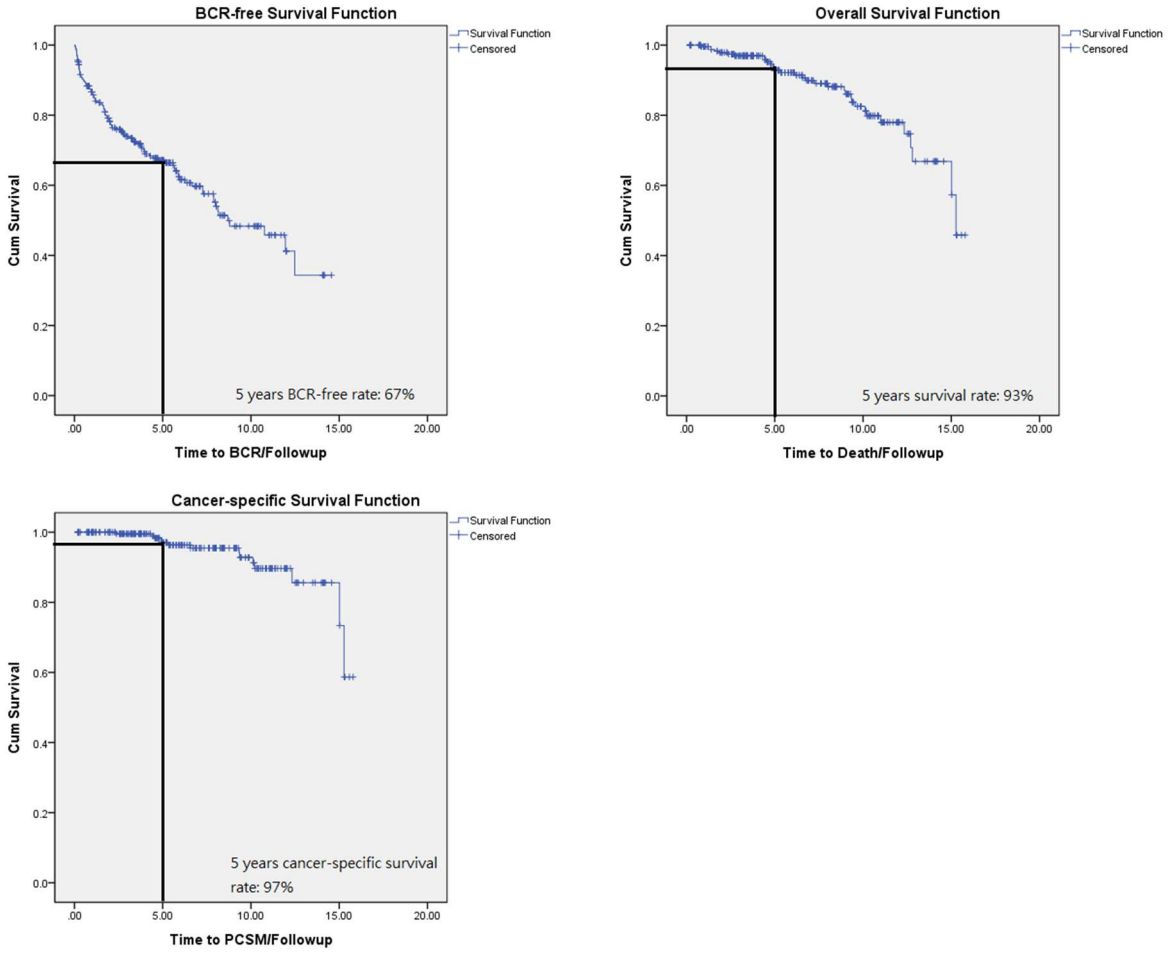


Table 6b: Outcomes comparison with EORTC 22911 (BCR-free, Overall survival and Cancer-specific survival)

	EORTC 22911		Our patients	
	ART group	No ART group	Unadjusted	Adjusted
Inclusion criteria	• Prostate cancer clinical stage T0–3 N0 M0 • Pathological stage pT2–3 N0, with at least one of the adverse features			
5 years BCR-free rate	79%	54%	69%	67%
5 years Survival rate	91%	92%	94%	93%
5 years PCSM-survival rate	98%	97%	98%	97%

Table 8a: Summary table on comparison of proportion (Unadjusted BCR-free, Overall survival and Cancer-specific survival)

	5 yrs BCR-free		5 yrs Overall Survival		5 yrs Cancer Survival	
EORTC						
ART group	79%		91%		98%	
No ART group		54%		92%		97%
UCI						
Unadjusted	69%	69%	94%	94%	98%	98%
Unadjusted p	0.0001	<0.0001	0.07	0.21	1	0.3

Table 8b: Summary table on comparison of proportion (Adjusted BCR-free, Overall survival and Cancer-specific survival)

	5 yrs BCR-free		5 yrs Overall Survival		5 yrs Cancer Survival	
EORTC						
ART group	79%		91%		98%	
No ART group		54%		92%		97%
UCI						
Adjusted	67%	67%	93%	93%	97%	97%
Adjusted p	<0.0001	<0.0001	0.24	0.54	0.27	1

3. Cost estimation for patients

In Table 9, SWOG trial patients in no ART group had urinary complication, SRT and hormonal therapy cost. The observation group had no patient experiencing rectal complication. ART, hormonal therapy, rectal bleeding and urinary toxicities management were included in treatment group. For internal estimation, ART and no ART patients spent $26,343 and $7,874 per patient, respectively. Most of our patients did not go through ART and therefore cost of secondary intervention in our clinic was about $3,544 per patient.

Table 9: Cost comparison with SWOG 8794 and UC Irvine observation patients

	SWOG 8794		Our patient group (N=364)
	No ART (N=211)	ART (N=214)	
ART cost	0	$24,548 per patients × 214 patients in trials	$24,548 per patients × 5 patients in our clinic
Complication cost	Urinary stricture cost &4,648 × 20 patients	a. Rectal bleeding cost $2,660 × 7 patients b. Urinary stricture cost $4,648 × 38 patients	0
Treatment cost	a. RT cost =$16,755 × 70 patients b. HT cost =$8,991 × 44 patients	HT cost =$8,991 × 21 patients	a. RT cost = $16,755 × 38 patients b. HT cost =$8,991 × 59 patients
Total Cost	$1,661,414	$5,637,327	$1,289,899
Cost per patient	$7,874	$26,343	$3,544

IV. DISCUSSION

1. Interpretation for the results

First, we used SWOG 8794 and EORTC 22911 inclusion criteria in our clinic to examine the resemblance of patient's formation. After selecting patients by trial's criteria, we counted the number of patients with BCR, OM and PCSM in tables. Only one third of patients had BCR and a very small proportion in OM and PCSM. Because of the difference of distribution in high risk group, we adjusted our patients by Gleason score and pathological stage before analyzing the outcomes. As a result, Kaplan-Meier graphs presented high survival rate for every outcomes, with the exception of the BCR-free rate.

In cost assessment, we did not separate our patient into treatment and control group when we estimated our cost. The reason why we kept it as one group was that only 5 patients underwent ART. If clinician or health care system wants to support ART, they would have to reduce half of ART cost for each patient or improve their survival rate outcomes. To sum up, our analysis shoes that both ART and observation patients have similar long-term clinical outcomes but had a huge difference on medical expense.

2. Radiotherapy timing and side effects

Because of the limited effect on oncological outcomes, radiotherapy timing is a controversial issue. Fossati and colleagues recruited 510 pT3 N0 post-operative patients. They separated patients to ART versus observation followed by SRT and clinical outcomes were metastasis-free rate and OM. Within 8 years follow-up, there was no significant difference for outcomes between groups. Therefore, SRT may reduce the overtreatment effect on adjuvant radiotherapy. [18] Also, Wallis and associates developed a decision

analysis model for ART against SRT. In their conclusion, they found the SRT group to have better quality-adjusted life expectancy than the ART group. [19] Even further, the recovery rate of erectile function and urinary function were evaluated for post-RP patients with or without radiotherapy by Zaffuto and associates. They also tested the outcomes with different radiotherapy timing in the adjuvant versus salvage setting. For 3 years follow-up on functional outcomes of erectile function and urinary continence, there were significant difference between SRT, ART and no radiation group: SRT had better maintenance of outcomes compared than ART. Their results proved that late post-operative radiotherapy timing with indication by BCR would provide improved functional outcomes, when compared to proliferative radiation based only on adverse pathological characteristics. [20]

Another question is the side effects and quality of life issues associated with radiotherapy. Gastrointestinal toxicity, genitourinary toxicity and sexual dysfunction could affect post-RP radiotherapy patient's life quality [30]. Of note, complication rates were higher in radiation group in both the SWOG and EORTC trial. [8, 10] Furthermore, Sineshaw et al. found that declining use of radiotherapy in their research, possible suggesting that clinicians may be increasingly concerned about side effects and insufficient evidence proving survival benefit. [21]

3. Effect on current guidelines

ART is suggested by current guidelines by the National Comprehensive Cancer Network, American Urological Association, and European Association of Urology [6, 30, 31] based on the benefit to PSA progression. [19] However, not only the advantage of ART on PSA should be weighed but also the possibility of side effects and quality of life influence has to be informed. [22] While two large-scale randomized control trials were focused on BCR-free

rate, neither of them could prove the achievement of benefit towards OM or PCSM. Trock and his research team tested prostate cancer-specific survival in SRT, no salvage treatment and SRT with hormonal therapy. They demonstrated disease-specific survival rate improvement on patients with SRT but the salvage treatment had to be given within 2 years of indication by BCR and PSA doubling time less than 6 months. [25] Our results and this article provide the suggestion that SRT may have similar or even better clinical and economic outcomes instead of ART. Regardless, after considering the toxicities, cost, and potential overtreatment via adjuvant radiation therapy, it appears that current guideline recommendations should be revised to a more conservative approach.

4. Limitation

The current study conclusions should be interpreted within the context of study design. First, our retrospective data was collected within 14 years post-radical prostatectomy, but we just had median follow-up 5.4 years. We kept contacting patients to obtain their information; however, some patients declined tracking regularly or did not follow-up with our clinic. However, 732 out of 1460 patients had follow-up beyond 5 years post-radical prostatectomy and it is well-known that the majority of recurrences occur within the first five years of surgery [32]. While follow-up can be continued to match randomized control trial's 10-year follow-up period, it is likely that the estimation of oncological outcomes in our study matches well with 10-year outcomes.

Second, we could not directly compare ART and observation group when we tried to analyze outcomes in our own data. This is largely due to the fact that adjuvant radiation therapy is not routinely prescribed at our institution. As such, we conducted a oncological outcomes analysis, finding that all comparisons were not statistical significantly different

between groups. In addition, every covariate, such as age, PSA, pathological T stage and risk factors, should be considered as a covariate when comparing oncological outcomes. To address this concern, we performed adjusted analysis and proportionately matched our patient cohorts to the demographics of the two randomized control trials. This analysis yielded consistent results.

Lastly, we can't have a conclusive evidence that if adjuvant therapy can completely remove from guidelines. Even though we did the patient's risk adjustment and get convincible data, we still need the large size and similar pathology of patient group to enhance our argument. Also, we don't have an ability to generalize our results on study population because UCI clinic patient's composition was different in many respects such as ethnic majority, education level and economic status.

V. FUTURE DIRECTION

In terms of future direction, we may also apply same analysis process on SRT and ART or observation group to test the clinical outcomes such as BCR, OM and PCSM. After the analysis, we will try to develop a consensus regarding the timing of post-operative radiotherapy. In addition to the two randomized control trials presented in this work, RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery) and RTOG 0534 (Radiation Therapy Oncology Group) are RCTs of SRT with or without ADT. Both trials will help in examining the effect of supplemental hormonal therapy. [27] Generally, since many researchers noticed that ART only have benefit on BCR-free rate, we are advocating the need to pay more attention to OM and PCSM. In addition to oncologic benefit, however, adverse events and side effects of radiotherapy should also be considered as important influence for patients. Three major RCTs give the recommendation on ART, but only the German trial used inclusion of criteria on patients with undetectable post-operative PSA. The others did not have specific requirements regarding post-surgical PSA. Even though they all state the PSA had better control after ART, the variety of trial's analysis methods could not provide support to radiation effect on BCR-free rate. In the future, we should design more detailed classification and analysis models to test the effect on radiotherapy after consulting with multidisciplinary experts. [26, 27]

For the limitation about comparing directly between groups, we will seek to develop radiation and observation group from the Surveillance, Epidemiology, and End Results (SEER) program. It can help us to build similar pathology for both groups.

VI. CONCLUSION

Radiotherapy after RP is suggested to improve clinical progression. However, The American, European and German trials are only advantageous in regards to PSA – outcomes of OM, metastasis-free survival, and prostate cancer survival are questionable in these studies. To further elucidate this effect, we demonstrate an oncological outcomes analysis by comparison between major RCTs and an internal cohort of radiation-naïve, observation patients. As a result, OM and PCSM in the trial's radiation group are non-inferior to our control group. Even further, it should be noted that only one-third of patients ever meet BCR.

In addition to oncologic outcomes, cost is another problem derived from overtreating patients without indication for radiation therapy. Treating patients who may not have BCR after surgery will bring about unnecessary expense and side effects. Even further, the reduction of cost can also take off some burden from the overall health care system. Since the current study found insufficient support for the clinical outcomes and excessive treatment cost, we advise to inform patients about both the advantage and disadvantage of adjuvant radiotherapy.

In summary, decision of early radiation treatment should be re-evaluated because of the lack of mortality benefit, disadvantage of radiotherapy and the cost.

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